Lymphoid regeneration from gene-corrected SCID-X1 subject-derived iPSCs.

Journal: Cell Stem Cell

Publication Year: 2015

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PubMed link: 25772073

Funding Grants: Masters of Science Specialization in Stem Cell Technology

Public Summary:
X-linked Severe Combined Immunodeficiency (SCID-X1) is a genetic disease that leaves newborns at high risk of serious infection and a predicted life span of less than 1 year in the absence of a matched bone marrow donor. The disease is due to mutations in the gene encoding hormone receptor on white blood cells, leading to a lack of functional lymphocytes, a type of white blood cells. Viral gene therapy to replace the mutated gene carries the risk of inducing leukemia, so there is a need to explore alternative therapeutic options. We have utilized induced pluripotent stem cell (iPSC) technology and genome editing to generate patient-specific mutant and gene-corrected iPSC lines. While the patient-derived mutant iPSCs have the capacity to generate blood stem cells and other white blood cell types, only normal and gene-corrected iPSCs can additionally generate mature lymphocytes that produce the correct form of the hormone receptor. This study highlights the potential for the development of cell therapy for SCID-X1 patients.

Scientific Abstract:
X-linked Severe Combined Immunodeficiency (SCID-X1) is a genetic disease that leaves newborns at high risk of serious infection and a predicted life span of less than 1 year in the absence of a matched bone marrow donor. The disease pathogenesis is due to mutations in the gene encoding the Interleukin-2 receptor gamma chain (IL-2Rgamma), leading to a lack of functional lymphocytes. With the leukemogenic concerns of viral gene therapy there is a need to explore alternative therapeutic options. We have utilized induced pluripotent stem cell (iPSC) technology and genome editing mediated by TALENs to generate isogenic subject-specific mutant and gene-corrected iPSC lines. While the subject-derived mutant iPSCs have the capacity to generate hematopoietic precursors and myeloid cells, only wild-type and gene-corrected iPSCs can additionally generate mature NK cells and T cell precursors expressing the correctly spliced IL-2Rgamma. This study highlights the potential for the development of autologous cell therapy for SCID-X1 subjects.